

Timing of quality of life assessment in cancer clinical trials: fine tuning remains a challenge

Over the past decades, hundreds of different quality of life-related measures have been published, including generic (general) and disease or treatment-specific measures to be used in cancer patients. ‘Just give me the best quality of life questionnaire’ is a familiar request to those involved in quality of life research, especially those collaborating with clinicians who conduct clinical trials. This simple question exposes a morass of complexity. Usually there is at least some empirical evidence to assist the choice, but that depends critically upon the research question and the corresponding study design.

In a recent phase-III trial by Saad et al. in hormone-refractory prostate cancer, patients receiving the bisphosphonate zoledronic acid experienced fewer skeletal-related events and a longer time until the first skeletal-related event as compared to those receiving placebo [1]. The skeletal-related events, comprising pathologic bone fractures, spinal cord compression, surgery and radiation therapy to bone or a change of antineoplastic therapy to treat bone pain, might reasonably be expected to impact on patients’ quality of life. Yet the investigators found no corresponding treatment differences in health-related quality of life as measured by three different types of validated questionnaires, a cancer-specific quality of life questionnaire (FACT-G) [2], a pain questionnaire (BPI) [3] and a health state profile (EuroQol) [4] at three months intervals.

These negative quality of life findings led to a questioning of the clinical relevance of skeletal-related events [5, 6]. Are quality of life measures really a valid and responsive measure relevant to this research question [7]?

Such results bolster the prejudices of those who think that measuring quality of life endpoints in cancer clinical trials is a mere tribute to political correctness. More than half a century ago, Karnofsky and Burchenal in their landmark paper enunciated the case for objective measurement: “... In the absence of coincident and significant objective evidence of a therapeutic effect, subjective improvement is a notoriously poor method of evaluating a therapeutic agent against cancer ...” [8]. As an alternative to a ‘subjective’ measure they introduced standardized measures of functional status which have influenced assessment of cancer patients ever since. In the study by Saad et al., despite the suggestion of benefit there was no statistically significant difference in ECOG performance status among the treatment groups.

In this issue of *Annals of Oncology*, Weinfurt and colleagues [9] present a secondary analysis of the data by Saad et al. They investigated the clinical relevance of skeletal-related events in terms of their impact on patients’

trajectories of quality of life, pain and health state preferences by assessing changes after each patient’s first skeletal-related event. Skeletal-related events appeared to have clinically meaningful effects on the different quality of life measures. The authors conclude that using fixed 3-month assessments, especially when the interval between visits is longer than it takes for the acute event to resolve, may not provide good estimates of the patient’s underlying trajectory. In this situation, it is unlikely that a sensitive treatment comparison can be made.

What should these considerations teach us for future trials? As Weinfurt and colleagues conclude, investigators designing trials involving repeated acute events should consider event-triggered data collection or more intensive, diary-type assessments. Event-triggered data collection is a new interesting strategy for cancer clinical trials. It may require close patient monitoring to capture the relevant events. Diaries have frequently been used in different clinical trial settings. Their responsiveness to symptoms and side-effects is well established. However, missing data is an issue [10]. Recent developments of electronic diaries such as self-report by palm-top or mobile phone short message service may overcome some of these difficulties and may also be used for event-triggered data collection. Such strategies raise new methodological questions [11], especially in defining a clinically meaningful difference from a longitudinal perspective.

From a clinical point of view we are interested in the patient’s overall experience of quality of life over the time of the relevant intervention, rather than in widely spaced single point estimates. Defining the appropriate assessment interval for this purpose is not trivial. In the trial by Saad et al., a monthly schedule might have resulted in a different conclusion regarding quality of life. The assessment interval depends not only on the question to be addressed and the clinical factors but also on practical and conceptual issues. A comprehensive quality of life assessment, considered as ‘best practice’ by many, might however involve multiple generic and disease- or treatment-specific measures (e.g., 30 to 50 questions) which may not be feasible in a confined clinical context. Especially in the palliative setting patient burden should be kept to a minimum both for humanitarian reasons and because it is a source of missing data.

Can we ‘keep it simple’ for frequently repeated assessments? Global indicators, such as for ‘quality of life’ itself [12, 13] or for being bothered by treatment-related difficulties [14], are responsive to the wide spectrum of reactions seen in patients on and off treatment and may detect changes on single dimensions, allowing for comparison across treatments. Indicators of the most important symptoms and side-effects may complement the picture to an extent feasible even for diaries. We do not have to reinvent the development of quality of life measures: we can rely on existing short forms.

Regular implementation of such strategies may allow for new insight into the pattern of morbidity and adaptation. For example, studies may explore why patients' quality of life scores may differ in variability across time rather than merely reporting mean levels. Similarly, it is possible to examine whether there are predictive factors for the subjective tolerance of toxic therapies (e.g., high dose chemotherapy). The ultimate goal of measuring quality of life endpoints is to empower patients' voices in treatment evaluation. This can only be reached when these measures are timed correctly: fine tuning remains a challenge.

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References

1. Saad F, Gleason DM, Murray R et al. Zoledronic Acid Prostate Cancer Study Group. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002; 94: 1458–1468.
2. Cella DF, Tulsky DS, Gray G et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993; 11: 570–579.
3. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994; 23: 129–138.
4. The EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16: 199–208.
5. Atkins CD. Re: A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2003; 95: 332.
6. Rosenthal M. Re: A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2003; 95: 332.
7. Saad F, Gleason DM. Response. *J Natl Cancer Inst* 2003; 95: 333–334.
8. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod CM (ed.): *Evaluation of chemotherapeutic agents*. New York: Columbia University Press 1949; 191–205.
9. Weinfurt KP, Li Y, Castel LD et al. The significance of skeletal-related events for the health-related quality of life of patients with metastatic prostate cancer. *Ann Oncol* 2005; 16: 579–584.
10. Fayers P. MRC quality of life studies using a daily diary card: practical lessons learned from cancer trials. *Qual Life Res* 1995; 4: 343–352.
11. Bolger N, Davis A, Rafaeli E. Diary methods: capturing life as it is lived. *Annu Rev Psychol* 2003; 54: 579–616.
12. Sloan JA, Loprinzi CL, Kross SA et al. Randomized comparison of four tools measuring overall quality of life in patients with advanced cancer. *J Clin Oncol* 1998; 16: 3662–3673.
13. de Boer AG, van Lanschot JJ, Stalmeier PF et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? *Qual Life Res* 2004; 13: 311–320.
14. Bernhard J, Maibach R, Thurlimann B et al. Patients' estimation of overall treatment burden: why not ask the obvious? *J Clin Oncol* 2002; 20: 65–72.